From the INTERNATIONAL SEARCHING AUTHORITY

# PATENT COOPERATION TREATY

REC'D 02 FEB 2006
PCT

To:
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# PCT

## WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

| | |
|---|---|
| Applicant's or agent's file reference: 27929 | Date of mailing (day/month/year): 31 JAN 2006<br>FOR FURTHER ACTION<br>See paragraph 2 below |
| International application No.: PCT/IL04/00477 | International filing date (day/month/year): 03 June 2004 (03.06.2004) |
| | Priority date (day/month/year): 09 June 2003 (09.06.2003) |
| International Patent Classification (IPC) or both national classification and IPC: IPC: A61K 39/395( 2007.01);C07K 16/00( 2007.01);G01N 33/53( 2007.01);C12N 5/12( 2007.01)<br>US Cl.: 424/130.1, 141.1; 435/7.1, 326; 530/387.1, 391.1 | |
| Applicant: INSIGHT BIOPHARMACEUTICALS, LTD. | |

1. This opinion contains indications relating to the following items:

- ☒ Box No. I — Basis of the opinion
- ☐ Box No. II — Priority
- ☐ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV — Lack of unity of invention
- ☒ Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI — Certain documents cited
- ☐ Box No. VII — Certain defects in the international application
- ☐ Box No. VIII — Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(*b*) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

| Name and mailing address of the ISA/ US | Date of completion of this opinion | Authorized officer |
|---|---|---|
| Mail Stop PCT, Attn: ISA/US<br>Commissioner for Patents<br>P.O. Box 1450<br>Alexandria, Virginia 22313-1450 | 08 December 2005 (08.12.2005) | Marianne DiBrino, Ph.D. |
| Facsimile No. (571) 273-3201 | | Telephone No. 571-272-1600 |

**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/IL04/004[illegible]

**Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | |
|---|---|---|
| Novelty (N) | Claims Please See Continuation Sheet | YES |
| | Claims Please See Continuation Sheet | NO |
| Inventive step (IS) | Claims Please See Continuation Sheet | YES |
| | Claims Please See Continuation Sheet | NO |
| Industrial applicability (IA) | Claims Please See Continuation Sheet | YES |
| | Claims Please See Continuation Sheet | NO |

2. Citations and explanations:

Please See Continuation Sheet

# WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International Application No
PCT/IL04/00477

**Supplemental Box**
In case the space in any of the preceding boxes is not sufficient.

V.1. Reasoned Statements:
The opinion as to Novelty was positive (Yes)with respect to claims 6-9, 29-32, 38-42, 44, 57-61, 63, 69, 76-80, 84, 96-100, 101-127, 147-151, 161-165, 169
The opinion as to Novelty was negative (No) with respect to claims 1-5, 10-28, 33-37, 43, 45-56, 62, 64-68, 71-75, 81-83, 87,128-146, 152-160, 166-168, 170, 171
The opinion as to Inventive Step was positive (Yes)with respect to claims 6-9, 29-32, 38-42, 57-61, 69-70, 76-80, 84, 96-100, 113, 123-127, 147-151, 161-165, 161-165, 169
The opinion as to Inventive Step was negative(NO) with respect to claims 1-5, 10-28, 33-37, 43-56, 62-68, 71-75, 81-83, 85-95, 101-112, 114-122, 128-146, 152-160, 166-168, 170, 171
The opinion as to Industrial Applicability was positive (YES) with respect to claims 1-171
The opinion as to Industrial Applicability was negative(NO) with respect to claims NONE

V. 2. Citations and Explanations:
Claims 1-171 meet the criteria set out in PCT Article 33(4), and thus meet industrial applicability because the subject matter claimed can be made or used in industry.

Claims 6-9, 29-32, 38-42, 44, 57-61, 63, 69, 76-80, 84, 96-100, 101-112, 113, 114-122, 123-127, 147-151, 161-165, 169 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the claimed antibodies and methods.

Claims 1-5, 10-28, 33-37, 43, 45-56, 62, 64-68, 71-75, 81-83, 87,128-146, 152-160, 166-168, 170, 171 lack novelty under PCT Article 33(2) as being anticipated by US 2002/00068061 A1 as evidenced by admissions in the description on pages4 at lines 18-27 and on page 32 at lines 17-26.

US 2002/00068061 A1 discloses polyclonal and monoclonal antibodies raised against human heparanase, pharmaceutical compositions thereof, said monoclonal antibodies being scFv (single chain), fragments such as Fab 2 or Fab 1, humanized or chimeric. US 2002/00068061 A1 discloses HP130 and HP129, hybridomas producing monoclonal antibodies, methods of treatment for autoimmune diseases, arthritis, graft rejection, angiogenesis, tumor cell proliferation or circulation, metastases, inflammatory disorder using monoclonal antibodies. US 2002/00068061 A1 discloses neutralizing anti-heparanase antibodies such as HP130 which was binds to the C-terminal portion of heparanase. US 2002/00068061 A1 discloses methods of preparing monoclonal anti-heparanase antibodies using hybridoma technology (see entire document).
US 2002/00068061 A1 discloses immobilized antibodies (on Western blots) that comprise labeled antibodies (indirectly labeled on Western blots). US 2002/00068061 A1 discloses a method of detecting heparanase by binding an anti-heparanase neutralizing antibody to the sample and detecting a decrease in activity.

The admissions in the description on pages4 at lines 18-27 and on page 32 at lines 17-26 are that SEQ ID NO: 1 is the major subunit of human heparanase, and that HP130 binds to an epitope within the C-terminus of heparanase and HP239 binds to an internal epitope of heparanase, respectively.

# WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No
PCT/IL04/00477

**Supplemental Box**
In case the space in any of the preceding boxes is not sufficient.

Claims 1-5, 10-28, 33-37, 43-56, 62-68, 71-75, 81-83, 85-95, 101-112, 114-122, 128-146, 152-160, 166-168, 170, 171 lack an inventive step under PCT Article 33(3) as being obvious over US 2002/00068061 A1 in view of US 6,177,545.

US 2002/00068061 A1 discloses polyclonal and monoclonal antibodies raised against human heparanase, pharmaceutical compositions thereof, said monoclonal antibodies being scFv (single chain), fragments such as Fab 2 or Fab 1, humanized or chimeric. US 2002/00068061 A1 discloses HP130 and HP129, hybridomas producing monoclonal antibodies, methods of treatment for autoimmune diseases, arthritis, graft rejection, angiogenesis, tumor cell proliferation or circulation, metastases, inflammatory disorder using monoclonal antibodies. US 2002/00068061 A1 discloses neutralizing anti-heparanase antibodies such as HP130 which was binds to the C-terminal portion of heparanase. US 2002/00068061 A1 discloses methods of preparing monoclonal anti-heparanase antibodies using hybridoma technology (see entire document).
US 2002/00068061 A1 discloses immobilized antibodies (on Western blots) that comprise labeled antibodies (indirectly labeled on Western blots). US 2002/00068061 A1 discloses a method of detecting heparanase by binding an anti-heparanase neutralizing antibody to the sample and detecting a decrease in activity.

US 2002/00068061 A1 does not disclose treating atherosclerosis or aneurysm with the anti-heparanase antibody, nor detecting the presence of heparanase in a sample using a labeled anti-heparanase antibody, wherein the label is an enzyme or a radioactive label, nor a method of detecting conditions recited in claims 88-95, 101-112 and 114-122.

US 6,177,545 discloses using heparanase specific antibodies for therapy for a human of a condition associated with expression of heparanase, for quantification (detection) of heparanase in a body fluid such as blood, or urine or in situ. US 6,177,545 discloses detecting heparanse in solid or hematopoietic tumors such as melanoma, bladder, liver, breast cancer, treating patients with these conditions, and treating renal disease, cancer and diabetes. US 6,177,545 discloses using enzymes or radioactive labels coupled to antibodies for detecting heparanase (see entire document).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have treated the conditions or detected heparanase by the methods disclosed by US 6,177,545 using the anti-heparanase monoclonal antibodies disclosed by US 2002/00068061 A1.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to treat patients using a neutralizing antibody as disclosed by US 2002/00068061 A1 and to detect heparanase in a variety of medical conditions as disclosed by US 6,177,545.